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Original Research

Differential Impact of Blood Pressure Control Targets on Epicardial Coronary Flow After Transcatheter Aortic Valve Replacement

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ABSTRACT

Background: The cause for the association between increased cardiovascular mortality rates and lower blood pressure (BP) after aortic valve replacement (AVR) is unclear. This study aims to assess how the epicardial coronary flow (ECF) after AVR varies as BP levels are changed in the presence of a right coronary lesion.
Methods: The hemodynamics of a 3D printed aortic root model with a SAPIEN 3 26 deployed were evaluated in an *in vitro* left heart simulator under a range of varying systolic blood pressure (SBP) and diastolic blood pressure (DBP). ECF and the flow ratio index were calculated. Flow index value <0.8 was considered a threshold for ischemia.
Results: As SBP decreased, the average ECF decreased below the physiological coronary minimum at 120 mmHg. As DBP decreased, the average ECF was still maintained above the physiological minimum. The flow ratio index was >0.9 for SBP ≥130 mmHg. However, at an SBP of 120 mmHg, the flow ratio was 0.63 ($p \leq 0.0055$). With decreasing DBP, no BP condition yielded a flow ratio index that was less than 0.91.
Conclusions: Reducing BP to the current recommended levels assigned for the general population after AVR in the presence of coronary artery disease may require reconsideration of levels and treatment priority. Additional studies are needed to fully understand the changes in ECF dynamics after AVR in the presence and absence of coronary artery disease.

ABBREVIATIONS

AVR, aortic valve replacement; BP, blood pressure; CAD, coronary artery disease; DBP, diastolic blood pressure; ECF, epicardial coronary flow; RCA, right coronary artery; SAVR, surgical aortic valve replacement; SBP, systolic blood pressure; TAVR, transcatheter aortic valve replacement.

Introduction

Aortic stenosis impacts 5% to 10% of the elderly population and is expected to double by 2050.[1] Aortic valve replacement (AVR), whether surgical AVR (SAVR) or transcatheter AVR (TAVR), is the only effective therapeutic procedure to address aortic stenosis.[2,3]

Although AVR was shown to be effective in reducing symptoms and improving survivability rates, many patients experience poor quality of life, rehospitalization, or death after 1 year.[4] Among other reasons, some hypothesize that residual high vascular afterload post-AVR in individuals with systemic hypertension prevents sufficient left ventricular unloading and reverse remodeling.[4] Hence, adequate blood pressure (BP) control is

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recommended after AVR to achieve full benefit. Lindman et al.[4,5] recently reported in 2 large populations of patients treated with TAVR or SAVR that achieving lower systolic and diastolic blood pressure (SBP, DBP, respectively)—in the range that is currently recommended as the optimal target in BP guidelines (SBP≤120-130mmHg and DBP≤80mmHg)[4,6,7]—is independently associated with increased all-cause mortality, cardiovascular mortality, and rehospitalization. Additionally, Perlman et al.[8] observed that postprocedural hypertension is associated with better prognosis after TAVR. The cause for this association between increased cardiovascular mortality rates, worse prognosis, and lower BP remains unclear.

Immediately after AVR, a sudden relief of afterload occurs leading to changes in BP levels and coronary perfusion.[9–11] It has been shown that right after AVR, coronary perfusion increases.[12] In the long run, these occurrences may change, which may lead to a potential consideration of different BP management strategies after AVR. The presence of a bioprosthetic valve will certainly impose a new hemodynamic interaction within the aortic root compared with the native valve, as shown in previous controlled *in vitro* studies.[13,14]

In a previous study,[15] we experimentally assessed the effect of SBP and DBP independently on epicardial coronary flow (ECF) variation and valve hemodynamics. We found that ECF decreased below the physiological minimum when BPs were in the recommended range. While this provides a possible explanation, the study was conducted using an idealized rigid aortic root model. Moreover, the experiment was conducted without considering any coronary lesions.

In this study, we recreated, using 3D printing, a patient's case with right coronary lesion who had undergone an AVR procedure, developed postprocedural hypertension, was prescribed antihypertensive medication, and suffered a subsequent myocardial infarction. The ECF and the flow ratio at various BP conditions were evaluated.

Materials and Methods

A 78-year-old male with severe aortic stenosis (mean gradient 40 mmHg) and an asymptomatic 80% stenosis of the right coronary artery (RCA) (Figure 1) underwent a successful TAVR with 26 mm SAPIEN 3 Ultra at Piedmont Hospital (Atlanta, GA, USA). The patient developed postprocedural elevated BPs that were lowered to 120/47 mmHg. Two hours after TAVR, the patient developed severe angina. Emergency coronary angiography was performed showing the unchanged severe RCA lesion. A successful RCA percutaneous coronary intervention was performed without complications.

Contrast-enhanced computed tomographic scans and echocardiographic images were received under an institutional review board-approved study between Piedmont and Michigan Technological University. From the computed tomographic scans, the patient-specific 3D digital model of the aorta, coronary arteries, and calcium lesions were generated and 3D printed at Mayo Clinic (Figure 2) similar to previous studies.[13,14,16–18]

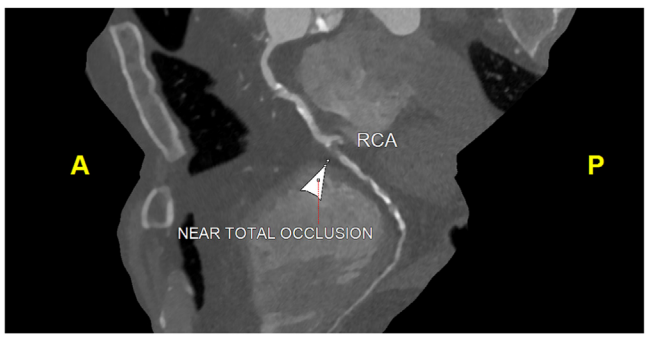

Figure 1. Location of the coronary lesion in the RCA.
Abbreviation: RCA, right coronary artery.

A 26 mm SAPIEN 3 Ultra (Edwards Lifesciences, Irvine, CA) was deployed into the model and hemodynamically assessed using a pulse duplicating left heart simulator (Figure 3). The left heart simulator is a pulse duplicating setup that comprises a reservoir (left atrium), a mitral valve at the exit of the reservoir, a bladder pump that represents the left ventricle, a flow sensor connected to the flowmeter to collect the average flow rate, the patient-specific aortic root chamber where the valve was deployed, a compliance chamber to emulate arterial compliance, and a gate valve to control the cardiac output. The bladder pump is controlled by a LabVIEW (National Instruments, Austin, TX) program to determine the desired heart rate and systolic-diastolic durations. As the artery of interest is the RCA in this experiment, we simulated the coronary flow as an extension from the patient's right coronary sinus back to the reservoir with a pinch valve (resistance) to control the flow rate. Patient-specific parameters (cardiac output = 4.9 L/min and heart rate = 60 bpm) were used in the experiment. In addition, different combinations of SBP and DBP were imposed, as shown in Figure 4. The SBP ranged from 120 to 150 mmHg and the DBP ranged from 60 to 100 mmHg.

Measurements of epicardial right coronary flow (ECF) variations with respect to time over 50 cardiac cycles were recorded using a Clamp-on flow sensor (Transonic Systems Inc, Ithaca, NY). Average ECF was between 58.8 and 73.5 ml/min, which is the physiological range for the RCA to achieve 70% of 4% to 5% of the total cardiac output.[15,19] The ECF was set within these physiological limits at 130/80 mmHg by setting the resistance of the coronary circuit at the beginning of the experiment. Then, once the baseline coronary conditions have been achieved, the coronary circuit parameters are held fixed as the systemic BPs are varied to evaluate the sole impact of aortic BP on the resulting coronary flow. In addition to instantaneous and averaged ECF measurement, the "flow ratio" index was computed. The flow ratio was defined as the ratio of coronary flow to the flow at the coronary ostium. The flow ratio is meant to measure the coronary flow along the coronary artery in the presence of a calcified lesion as a fraction of the flow at the ostium. Similar to the fractional flow reserve, we estimate 0.8 as a threshold for myocardial ischemia.[20]

All measurements were given as mean ± standard deviation. Statistical analysis was performed using JMP Pro 16.0 (SAS Institute Inc, Cary, NC). Normally distributed data was assessed using ANOVA followed by a Tukey test. Non-normally distributed data was assessed using Wilcoxon/Kruskal-Wallis test followed by a post hoc Dunn.

Results

The resulting ensemble-averaged right coronary flow waveforms as SBP and DBP varied are shown in Figures 4a and 5b, respectively. The right coronary flow waveform is known to not be impacted by the intramyocardial vessel compression, unlike the left coronary flow waveform, and therefore does not exhibit any biphasic pattern. As SBP decreases, the coronary flow decreases. As DBP decreases, more fluctuations are seen on the waveforms, especially during systole; however, the decrease in the diastolic portion of the coronary flow is more notable and consistent.

To evaluate the differences over the whole cardiac cycle, Figure 5a and 5b show the average coronary flow for each of the pressure conditions as SBP and DBP increase, respectively. As SBP decreases from 150 to 120 mmHg, the average coronary flow decreases from 64.78 ± 0.37 ml/min to 37.67 ± 0.29 ml/min. The average coronary flow at 120/80 mmHg is the only value that was found to be below the physiological minimum of 58.8 ml/min. Figure 5b shows that as DBP decreases from 100 to 60 mmHg, the average ECF is still maintained above the physiological minimum of 58.8 ml/min.

The resulting flow ratio index for the total cardiac cycle is >0.9 at an SBP of 130 and 150 mmHg (Figure 6a). However, at an SBP of 120 mmHg,

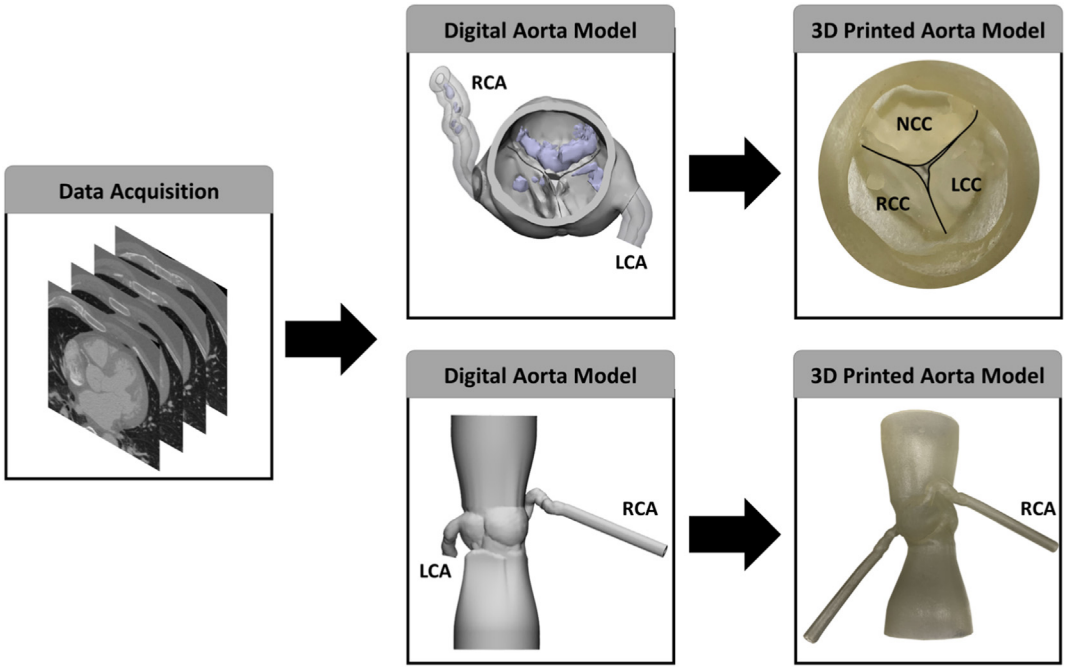

Figure 2. Patient-specific model generation and 3D printing workflow.
Abbreviations: LCA, left coronary artery; LCC, left coronary cusp; NCC, noncoronary cusp; RCA, right coronary artery; and RCC, right coronary cusp.

the flow ratio is 0.63 ($p \leq 0.0055$). When DBP decreases, there is no BP condition that yields a Flow Ratio index that is less than 0.91 (Figure 6b).

Discussion

In this study, we conducted an *in vitro* experiment using a 3D printed patient-specific aortic root model to assess how epicardial coronary flow after TAVR varies with dynamic BP changes in the presence of a fixed right coronary stenosis.

Current guidelines for BP regulation (SBP≤120-130 mmHg and DBP≤80 mmHg)[4,6,7] are designed to provide general guidance for general populations of patients, and do not account for specific scenarios such as patients who underwent AVR.[21,22] The need to consider these guidelines for AVR patients was raised in multiple studies,[4,5,8] as

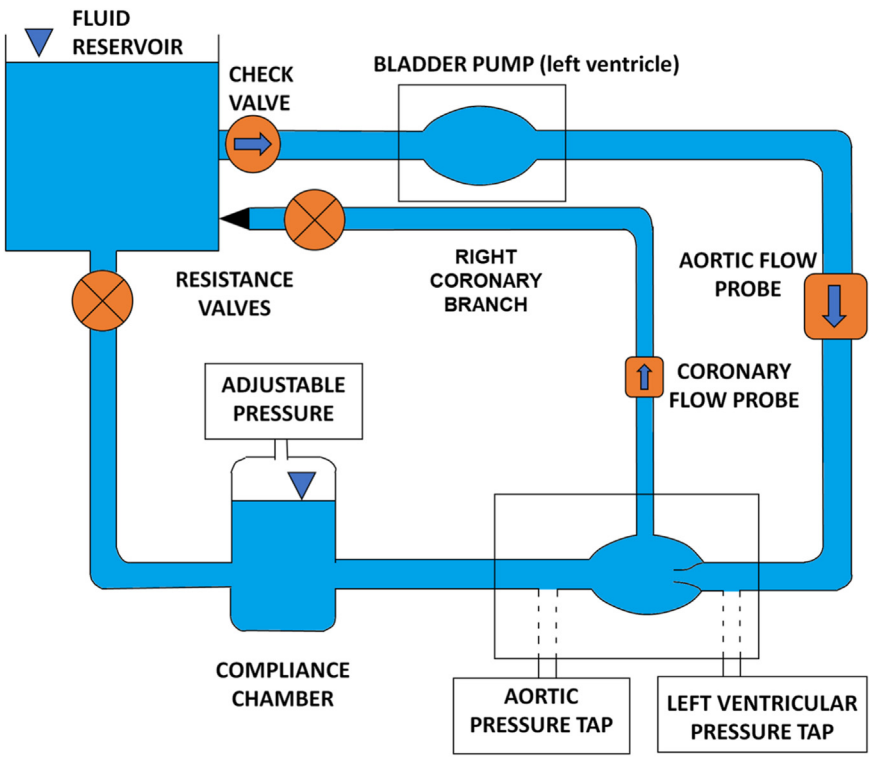

Figure 3. Schematic showing the *in vitro* left heart simulator pulse duplicating flow loop.

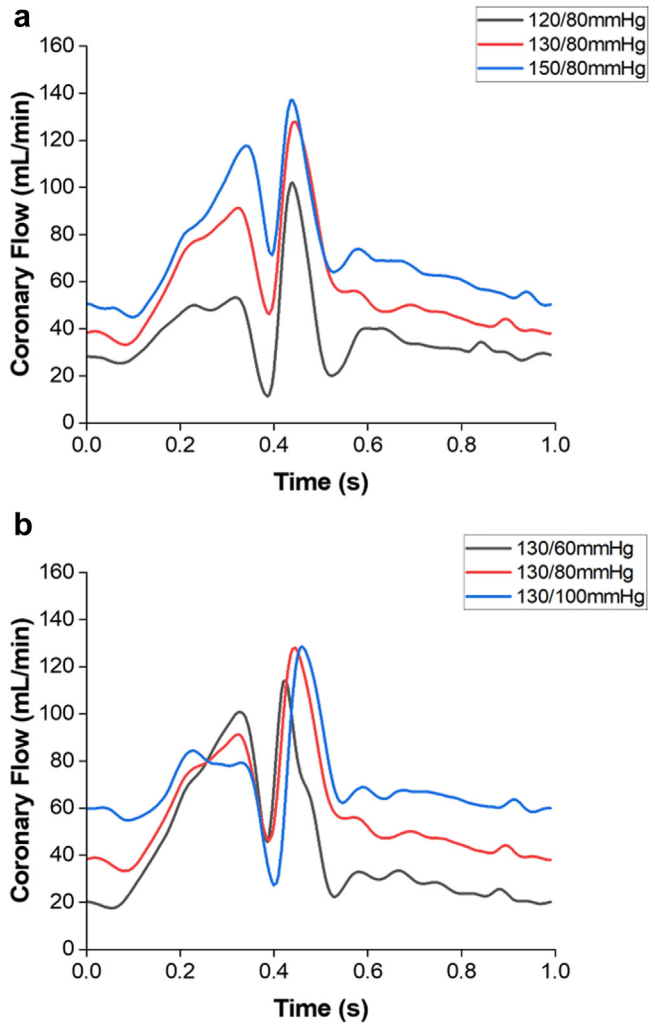

Figure 4. Ensemble averaged right coronary flow waveforms at different pressure conditions of (a) increasing SBP and (b) increasing DBP.
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

achieving the BP levels recommended by the guidelines in these patients was associated with increased all-cause and cardiovascular mortality. Nonetheless, the mechanisms leading to these worse outcomes with guideline-directed BP control are not well understood.

In this study, we found that an ideal guideline-directed BP target of 120/80 mmHg was associated with reduced ECF and flow ratio index, while higher BP values were associated with higher flow ratios (>0.9) for the same degree of coronary stenosis. The Flow Ratio is an index that can measure the maximum achievable myocardial blood flow in the presence of a coronary artery stenosis as a percentage of the maximum blood flow in the hypothetical case of a completely normal artery. A plausible explanation to these findings is the change in sinus flow patterns that occurs after AVR,[13,14,23] due to the new adjustment and interaction between the surrounding anatomy and the bioprosthetic valve. It is well known that as pressure decreases while coronary stenosis is constant, ECP will be expected to subsequently decrease. However, this case illustrates a complex relationship between BP control and coronary flow in the presence of coronary stenosis. Even when the BP is lowered to reach the "still physiological" recommended levels, the coronary flow levels may become non-physiological after AVR.

This work also raises the need to carefully consider subclinical or clinical coronary artery disease (CAD) in patients referred for valve replacement. Several studies support the importance of optimizing BP control following SAVR or TAVR to improve long-term outcomes.[11]

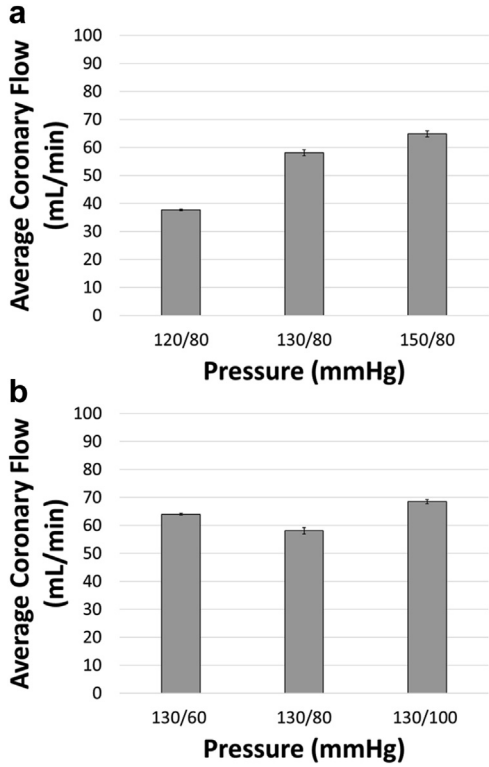

Figure 5. Average epicardial coronary flow values for the different pressure conditions of (a) increasing SBP and (b) increasing DBP. Values are reported as mean ± standard deviation.
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

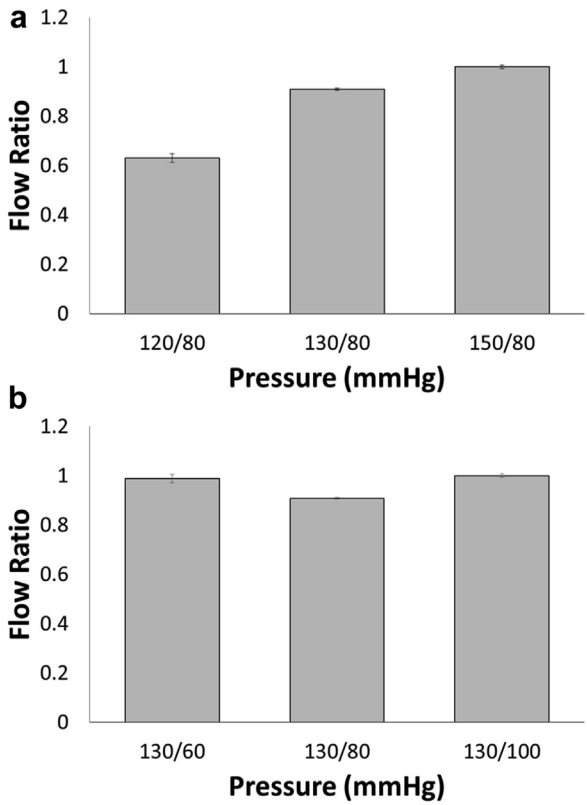

Figure 6. Flow ratio values for the different pressure conditions of (a) increasing SBP and (b) increasing DBP. Values are reported as mean ± standard deviation.
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

Reducing BP to the normal recommended values may possibly be detrimental only in the immediate postprocedural period, that is, before the regression of left ventricular hypertrophy and potential occurrence of diastolic dysfunction, and only in patients with significant obstructive CAD. This leads to potentially reconsidering the optimal strategy in such patients who develop hypertension following TAVR in regard to treating the CAD first and then controlling BP rather than leaving both hypertension and CAD untreated. Clearly, there is a combination of factors that influence these strategies, and further studies are necessary before guidelines may be developed.

Limitations

This study has several limitations. The *in vitro* setup used in the experiments does not simulate the coronary reserve; it is, however, an appropriate model to represent epicardial coronary flow, which is the variable of interest in this manuscript. Additionally, this *in vitro* setup accurately represented myocardial contraction in previous studies.[16,19,23] Moreover, this study was performed using a single-patient model. Hence, our findings should be viewed as hypothesis-generating and should prompt further research to address the open regarding optimal BP management peri-AVR in the presence of coronary disease.

Conclusions

Guideline-recommended BP targets may not be appropriate for patients with untreated coronary disease who have undergone TAVR. Epicardial coronary flow in such patients is affected by factors that do not exist in the general population such as the patterns of neo-aortic sinus flow. Additional studies are needed to fully understand the changes in ECF dynamics after AVR in the presence and absence of coronary artery disease.

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Ethics Statement

The research reported has adhered to the relevant ethical guidelines. The study was performed under an institutional review board-approved study between Piedmont and Michigan Technological University.

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Disclosure Statement

The authors report no conflict of interest.

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